ORGANIC LETTERS

1999
Vol. 1, No. 4
537−539

An Unprecedented Nitrogen Elimination Reaction: Mechanistic Studies Using ^{15}N-Labeled 4-Amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile

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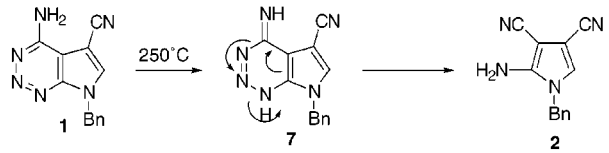
Received March 18, 1999

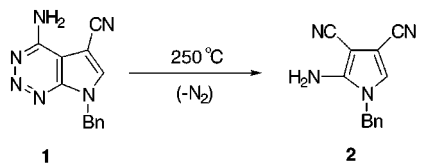
ABSTRACT



In the course of our work on novel pyrrolo[2,3-*d*][1,2,3]triazines we have discovered that 1 undergoes an elimination of nitrogen at 250 °C to give 2. We have conducted ^{15}N labeling studies that establish that the loss of N-2 and N-3 from 1 had occurred rather than N-1 and N-2, presumably via a retro Diels–Alder reaction of the imino tautomer 7. This study provides an alternative to the commonly accepted mechanism which involves the loss of N-1 and N-2 via the transient formation of a diazonium compound generated from 4-amino- or 4-oxo-substituted 1,2,3-triazines condensed with carbocycles or heterocycles.

We have been involved for several years in studies[1] on the synthesis and chemical reactivity of various heterocycles as analog of the purine ring system. A recent literature search for derivatives of the pyrrolo[2,3-*d*][1,2,3]triazine ring system revealed the existence of only two examples of this ring system. The synthetic approach used for the preparation of these two examples[2] was very restrictive since it provided only a limited choice of exocyclic functional groups. This prompted us to develop new methodology[3] to obtain a versatile pyrrole intermediate that could provide pyrrolo-[2,3-*d*][1,2,3]triazines with a wide choice of exocyclic groups. We are currently[4] using this approach for the design and synthesis of a chemically diverse group of pyrrolo[2,3-*d*][1,2,3]triazines in order to study the chemistry of this essentially unexplored ring system. In the course of these studies, we observed that one of these derivatives, 4-amino-7-benzylpyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**1**), underwent a rapid gas evolution at its melting point to afford an amber liquid which solidified on cooling to room temperature. This solid was subsequently identified[5] as 2-amino-1-benzylpyrrole-3,4-dicarbonitrile (**2**) (Scheme 1). A literature search revealed that most 4-amino- or 4-oxo-substituted 1,2,3-triazines, condensed with a carbocycle or a heterocycle,

Scheme 1



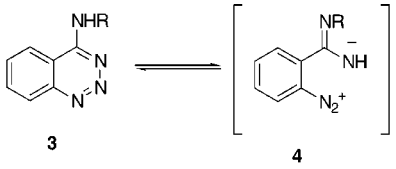
(1) (a) Zhu, Z.; Saluja, S.; Drach, J. C.; Townsend, L. B. J. *Chin. Chem. Soc.* **1998**, *45*, 465. (b) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1998,** *63*, 984. (c) Marakos, P.; Pouli, N.; Wise, D. S.; Townsend, L. B. *Synlett* **1997**, *5*, 561. (d) Swayze, E. E.; Townsend, L. B. *J. Org. Chem.* **1995**, *60*, 6309. (e) Krawczyk, S. H.; Townsend, L. B.; *Tetrahedron Lett.* **1991,** *32*, 5693. (f) Beylin, V. G.; Townsend, L. B. *J. Heterocycl. Chem.* **1988**, *25*, 97. (g) Acevedo, O. L.; Krawczyk, S. H.; Townsend, L. B. *J. Heterocycl. Chem.* **1985**, *22*, 349. (h) Chung, F.-L.; Earl, R. A.; Townsend, L. B. *J. Org. Chem.* **1980**, *45*, 2532. (i) Schram, K. H.; Manning, S. J.; Townsend, L. B. *J. Heterocycl. Chem.* **1975**, *12*, 1021. (j) Schram, K. H.; Townsend, L. B. *Tetrahedron Lett.* **1974**, 1345. (k) Long, R. A.; Gerster, J. F.; Townsend, L. B. *J. Heterocycl. Chem.* **1970**, *7*, 863.

(2) (a) Roth, H. J.; Eger, K. *Arch. Pharm. (Weinheim, Ger.)* **1975**, *308*, 186. (b) Steinhilber, D.; Schmidt, K.; Eger, K.; Roth, H. J. *Pharm. Res.* **1986**, *3*, 271.

10.1021/ol990006x CCC: $18.00
Published on Web 07/24/1999

underwent reactions that were explained by the transient formation of a diazonium compound (Scheme 2).[6] For

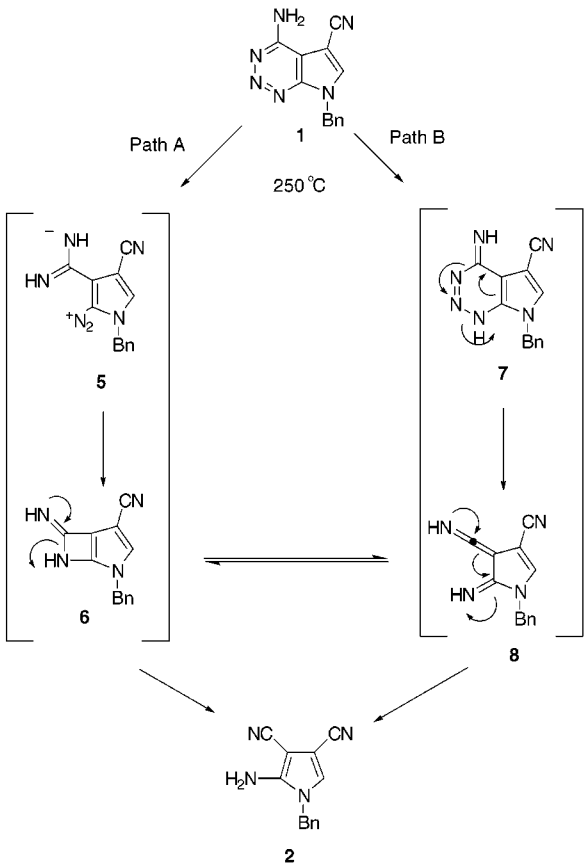
Scheme 2



example, the products isolated by hydrolysis or pyrolysis of substituted 4-aminobenzo-1,2,3-triazines (**3**) were explained in terms of the transient intermediate **4**.[7] The behavior of these and other fused 1,2,3-triazines is consistent with the loss of nitrogen from the N-1 and N-2 positions either through a diazonium intermediate[8,9] or a radical pathway.[8]

These previously reported results would suggest a mechanism for the conversion of compound **1** to compound **2** that involves the loss of N-1 and N-2 through the transient diazonium compound **5**. This would be followed by the loss of nitrogen and the formation of **6**. A subsequent collapse of compound **6** would afford the pyrrole **2** with an overall loss of N-1 and N-2 and a transfer of the N-3 of pyrrolotriazine **1** to the 2-position of pyrrole **2** (Scheme 3, path A).

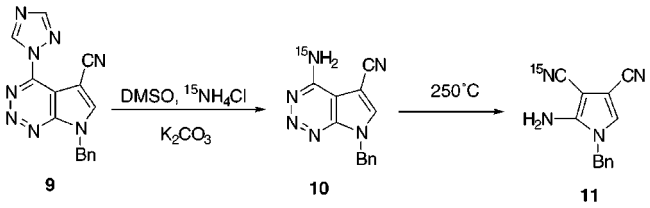
Scheme 3



However, we also considered the possibility of an alternative mechanism for the formation of pyrrole **2** from pyrrolotriazine **1** (Scheme 3, path B) that would involve a retro Diels–Alder reaction resulting in the loss of N-2 and N-3 from the imino tautomer **7** to give a tautomer (i.e., **8**) of pyrrole **2**.

Because a mechanism which involved a loss of N-2 and N-3 was unprecedented, we initiated some ^{15}N labeling studies to determine which of these two possibilities was occurring. Treatment of 7-benzyl-4-(1,2,4-triazol-1-yl)pyrrolo[2,3-*d*][1,2,3]triazine-5-carbonitrile (**9**)[10] with $^{15}NH_4Cl$[11] and K_2CO_3 in DMSO gave compound **10**.[12] Heating pyrrolotriazine **10** to 250 °C neat under argon gave the ^{15}N-labeled pyrrole **11**[13] (Scheme 4). ^{15}N NMR and ^{13}C NMR confirmed

Scheme 4



that a product containing only a label at the 3-CN position was obtained, i.e., a cyano resonance at 115.2 ppm was observed as a doublet (J = 18 Hz), indicating a ^{15}N-3-CN/^{13}C-3-CN coupling, while a resonance for the 4-CN group was observed as a singlet at 115.1 ppm in the ^{13}C NMR spectrum of compound **11**. A resonance for C-2 of compound **11** in the ^{13}C NMR spectrum was observed as a singlet, indicating that the transfer of ^{15}N label to the 2-amino group had not occurred. Additionally, only one ^{15}N NMR resonance of compound **11** was observed in the cyano region at 263 ppm. Since the mechanism following path A involves an

(3) Migawa, M. T.; Townsend, L. B. *Synth. Commun.*, accepted for publication.

(4) Migawa, M. T.; Townsend, L. B. *J. Org. Chem.*, submitted for publication.

(5) Compound **1**: mp 225–226 °C; R_f = 0.18 (50% EtOAc/hexanes); ^1H NMR (DMSO-d_6, 300 MHz) δ 8.68 (s, 1H, ArH), 7.43 (s, 2H, D_2O exchangeable, NH_2), 7.33 (m, 5H, Ph), 5.59 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.8, 146.1, 138.2, 136.2, 128.8, 128.1, 127.7, 114.3, 98.7, 81.8, 48.8. Anal. Calcd for $C_{13}H_{10}N_6$: C, 62.39; H, 4.03; N, 33.58. Found: C, 62.21; H, 4.08; N, 33.31. Compound **2**: mp 199–201 °C; R_f = 0.51 (5% MeOH/chloroform); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.4–7.3 (m, 6H, ArH), 7.17 (m, 2H), 6.63 (s, 2H, D_2O exchangeable, NH_2), 5.06 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 148.4, 136.2, 129.1, 128.2, 127.5, 125.8, 115.5, 115.1, 90.6, 70.1, 48.8; IR (KBr) 3389–3219, 2217, 1655 cm^{-1}. Anal. Calcd for $C_{13}H_{10}N_4$: C, 70.26; H, 4.54; N, 25.21. Found: C, 70.13; H, 4.82; N, 25.31.

(6) *The Chemistry of 1,2,3-Triazines and 1,2,4-Triazines, Tetrazines, and Pentazines*; Neunhoeffer, H., Ed.; Wiley: New York, 1978.

(7) Stevens, H. N. E.; Stevens, M. F. G. *J. Chem. Soc.* **1968**, 765.

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(10) Compound **9**: mp 238–240 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 9.85 (s, 1H), 9.32 (s, 1H), 8.61 (s, 1H), 7.4–7.3 (m, 5H, Ph), 5.81 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 154.3, 149.5, 145.7, 144.6, 144.4, 135.4, 128.9, 128.3, 128.0, 114.2, 103.1, 85.1, 49.5. Anal. Calcd for $C_{15}H_{10}N_8$: C, 59.60; H, 3.33; N, 37.07. Found: C, 59.69; H, 3.49; N, 37.21.

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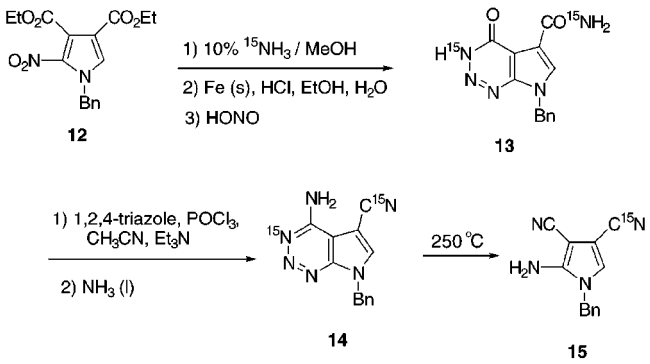
intermediate that would be expected to be symmetrical about the 3-position, it seems unlikely that this intermediate would fully retain its configuration about the 3-position, and scrambling of the label would be expected to result in the formation of pyrrole **2** labeled at the 3-CN and 2-NH_2 positions.

To unequivocally establish that N-2/N-3 bond cleavage was occurring, the preparation of labeled pyrrolotriazine **14** was accomplished from **12** (Scheme 5) using our established

Scheme 5



procedures.[4] Thermolysis of compound **14** at 250 °C provided labeled pyrrole **15**.[14] The structure was determined by proton-coupled ^{15}N NMR, which shows only one singlet at 258.5 ppm (relative to benzamide set at 100 ppm), indicating the presence of label only at the 4-CN position. This structure assignment for labeled pyrrole **15** is consistent with nitrogen extrusion from 7-substituted 4-aminopyrrolo-[2,3-*d*][1,2,3]triazines following path B.

It has not escaped our attention that this mechanism may be generally applicable to other fused 4-amino-1,2,3-triazines and could offer an alternative explanation of the reactivity of these compounds. However, a careful consideration must be made in each case when evaluating mechanisms involving the loss of N_2 from a fused 1,2,3-triazine.

Acknowledgment. We thank Ms. Kimberly Barrett for help in the preparation of this manuscript. This research was supported by Research Grants U19-AI-31718 and 5-RO1-AI-36872 from the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

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(12) Compound **10** was identical with **1** by ^1H NMR: ^{15}N NMR (DMSO-d_6, 50 MHz) δ 75.4 (t, J = 89 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 152.8 (d, J = 21 Hz), 146.1, 138.2, 136.2, 128.8, 128.1, 127.7, 114.3, 98.6 (d, J = 3 Hz), 81.8, 48.8.

(13) Compound **11** was identical with **2** by ^1H NMR: ^{13}C NMR (DMSO-d_6, 75 MHz) δ 148.4, 136.2, 129.1, 128.2, 127.5, 125.8, 115.2 (d, J = 18 Hz), 115.1, 90.6, 70.0 (J = 2.8 Hz), 48.8; ^{15}N NMR (DMSO-d_6, 50 MHz) δ 263 (s).

(14) Compound **13**: ^{15}N NMR (DMSO-d_6, 50 MHz) δ 230.8 (m), 104.5 (t, J = 89 Hz). Compound **14** was identical to compound **1** by ^1H NMR and ^{13}C NMR:^{15}N NMR (DMSO-d_6, 50 MHz) δ 326.3 (s), 261.3 (s). Compound **15** was identical to **2** by ^1H NMR and ^{13}C NMR: ^{15}N NMR (DMSO-d_6, 50 MHz) δ 258.5 (s).